Two-Year Performance and Safety Results of the MINIject Supraciliary Implant in Patients With Primary Open-Angle Glaucoma: Meta-Analysis of the STAR-I, II, III Trials

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• PURPOSE: To evaluate the performance and safety of minimally invasive glaucoma surgery with a supraciliary drainage device (MINIject; iSTAR Medical, Wavre, Belgium) in primary open-angle glaucoma (POAG) as a stand-alone procedure.

• DESIGN: Meta-analysis.

• METHODS: At 11 sites in Colombia, France, Germany, India, Panama, and Spain, 82 patients were treated in 3 prospective, multicenter, interventional, nonrandomized trials (STAR-I, II, III). Data were pooled in a meta-analysis of up to 2 years of follow-up postimplantation. The main outcome measures were mean relative and absolute reduction in diurnal intraocular pressure (IOP) compared to baseline. Secondary outcomes included patients with IOP ≤18 mmHg, patients with IOP reduction ≥20%, number of IOP-lowering medications, adverse events, and endothelial cell density loss.

• RESULTS: At the 2-year follow-up (n = 66), mean IOP was reduced from 23.8 ± 3.3 mmHg at baseline to 14.4 ± 4.5 mmHg (−39.3%; $P < 0.0001$). An IOP reduction of ≥20% was achieved in 89.4% of patients, with 84.8% having an IOP ≤18 mmHg. IOP-lowering medications were reduced from a mean of 2.4 ± 1.1 to 1.4 ± 1.4 ($P < 0.0001$), with 37.9% of patients being medication-free at 2 years. Mean endothelial cell density loss at 2 years was 6.2 ± 9.1% compared to baseline and no patient had a loss >30%.

• CONCLUSIONS: This meta-analysis demonstrates the favorable safety and efficacy profile of a supraciliary device implanted in a stand-alone, ab-interno procedure in patients with mild-to-moderate POAG. The data demonstrate that MINIject is a safe and effective, bleb-free treatment option for patients requiring low target IOP up to 2 years. (Am J Ophthalmol 2024;260: 172–181. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

Accepted for publication December 10, 2023.

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INTRODUCTION

Glaucoma is a group of complex eye diseases leading to chronic and progressive damage to the optic nerve and irreversible vision loss.[1,2] At present, reducing intraocular pressure (IOP) is the only proven method to prevent the development or progression of glaucoma and protect optic nerve fibers from further glaucomatous damage.[3,4] Surgical therapies such as trabeculectomy or tube shunt implantation are well-established, highly invasive treatments for IOP reduction when medical therapy and/or selective laser trabeculoplasty intervention fail to achieve satisfactory results, or in cases when initial presentation is of advanced glaucoma.[5-7] These glaucoma surgeries lower IOP effectively, but significant rates of procedure-related complications such as hypotony and bleb-related complications such as blebitis can occur.[8,9]

Minimally invasive glaucoma surgery (MIGS) offers a safe, effective, and less invasive intervention for patients suffering from glaucoma.[10-15] The goal of MIGS is to provide meaningful IOP reduction in a safe and standardized manner. This typically leads to a reduction in the burden of ocular hypotensive medication (OHM), and reduces the need for traditional incisional glaucoma surgery.[9,12,16] Further advantages compared to traditional incisional glaucoma surgeries are reduced risks of surgical complications, eliminating the need to manage a bleb, and shorter re-

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2023.12.006

covery time.[17,18] MIGS devices that target the uveoscleral drainage pathway via the supraciliary space may be able to achieve more powerful IOP reduction than via the conventional outflow pathway.[8,11] Reduction in IOP via the conventional outflow pathway can be limited by the episcleral venous pressure, scarring or herniations within Schlemm's canal, and the absence of functioning collector channels.[15,19-24] The supraciliary space by its nature is not affected by these limitations, and still provides a natural outflow pathway contrary to procedures targeting the subconjunctival space.

Leveraging this mechanism of action, the CyPass Microstent (Alcon, Vernier-Geneva, Switzerland), a suprachoroidal MIGS implant, demonstrated significant IOP reductions when implanted both in combination with cataract surgery[25] and stand-alone,[12,26,27] and was both FDA-approved and received CE-Marking in Europe. However, the manufacturer voluntarily withdrew the implant from the global market in 2018 due to concerns with long-term endothelial cell density (ECD) loss.[28,29]

The MINIject supraciliary MIGS implant (iSTAR Medical SA, Wavre, Belgium) is made of a soft and flexible silicone matrix for improved biocompatibility. The implant and the material have been described previously in clinical and preclinical studies.[13-15,30-33] The STAR-I,[13,14] STAR-II,[15] and STAR-III studies were prospective, multicenter, interventional, nonrandomized, single-arm trials conducted to assess the safety and efficacy of MINIject in patients with open-angle glaucoma (OAG) uncontrolled by topical hypotensive medication. In this study, patient data from these 3 trials were pooled, and a meta-analysis was conducted to assess performance and safety outcomes in a larger population with up to 2 years of follow-up.

METHODS

Patients enrolled in the 2 prospective, nonrandomized, multicenter, interventional trials (clinicaltrials.gov - STAR-I: NCT03193736, STAR-II: NCT03624361, STAR-III: NCT03996200) were treated at 11 sites in Colombia, France, Germany, India, Panama, and Spain. All related MINIject study protocols were prospectively approved by the National Competent Authorities of each country, the responsible ethics committee at each hospital, and adhered to the tenets of the Declaration of Helsinki. All subjects provided written informed consent before any study procedures were undertaken, and all data were monitored on site by independent monitors.

The MINIject implant is a 5 mm long drainage device made of STAR material: a soft, flexible, medical grade silicone in a micro-porous network design which adapts to the eye anatomy. The 27 µm hollow sphere geometry results in the implant comprising one-third silicone and two-thirds empty space, enabling the flow of fluid through the implant and along its entire length. Preclinical studies have shown that the material used is biocompatible and causes minimal inflammation and fibrosis.[13,30] MINIject obtained CE-marking in late 2021. The same MINIject implant has been used in all 3 studies of this meta-analysis, although the system used to deliver the implant has evolved.

Across the trials, uniform patient clinical data were collected preoperatively and at 1 day, 1 and 2 weeks, and 1, 3, 6, 12, 18, and 24 months postoperatively. All study subjects were adults (>18 years in STAR-I and STAR-III, >50 years in STAR-II), and had a complete ophthalmic examination including Goldmann applanation tonometry, best-corrected visual acuity (BCVA), gonioscopy, vertical cup/disc ratio, slit-lamp examination, dilated funduscopic ophthalmoscopy, pachymetry, perimetry, and ECD measurements. All concomitant ophthalmic medications, demographic data, and medical history were recorded. There was no medication washout at any time point in the trials. After surgery, assessment of implant position by ultrasound biomicroscopy (UBM) was performed.

Inclusion criteria included a diagnosis of OAG (STAR-I and STAR-III) or POAG (STAR-II) with Shaffer Grade 3 or 4 on gonioscopy, although no patient in the trials included in this meta-analysis was diagnosed with secondary open angle glaucoma. Patient lens status could be phakic or pseudophakic, but patients had to be resistant or intolerant to treatment with topical hypotensive medication and have a medicated IOP between 21 and 35 mmHg. Exclusion criteria included diagnosis of glaucoma other than OAG, prior glaucoma surgery in the study eye other than argon or selective laser treatment performed ≥90 days prior to baseline visit, visual field defect in the central 10-degrees, or any clinically significant ocular pathology other than OAG. Additional exclusion criteria specific to the STAR-II trial included hypersensitivity to medical silicone, allergy to fluorescein, anterior chamber depth of the eye being inadequate for implantation, and ECD <1500 cells/mm². Only one eye per participant was enrolled. If both eyes met eligibility criteria, the study eye was selected by the investigator.

Each clinical site used its standard course of postoperative medications. Postoperatively, topical IOP-lowering medications were restarted as needed based on the investigator's discretion. The study methodology and surgical procedure have been described in more detail previously.[13-15] MINIject was implanted into the supraciliary space in a stand-alone procedure in all studies.

In this meta-analysis, the primary outcome measure was the relative and absolute reduction in diurnal IOP with or without the use of concomitant OHM at 24-month follow-up compared with baseline. Secondary outcome measures included the reduction of OHMs from baseline, number of patients with ≥20% reduction in diurnal IOP compared to baseline, number of medication-free patients, and patients with diurnal IOP ≤18 mmHg at 6, 12, 18, and 24-month follow-up. Qualified success was defined as diurnal IOP ≤ 21 mmHg and >5 mmHg with a ≥20% reduction in diur-

nal IOP from baseline, regardless of the use of OHMs. Complete success was defined similarly but without the use of OHMs. All performance analyses were conducted on both the modified intent-to-treat (mITT) patient population (all patients who received the implant and had measurements recorded for all predefined visits) and the per-protocol (PP) patient population (excluding patients with major protocol deviations including secondary glaucoma surgery after MINIject implantation). Safety outcomes included the assessment of frequently reported adverse events (AEs) and the mean reduction of central ECD at 6, 12, 18, and 24-month follow-up. Adverse events were adjudicated by an independent safety monitor for relatedness to the device or procedure and were reported as defined in the protocol. Patients were included in the ECD analysis if they fulfilled the following criteria: no change in specular microscopy equipment between baseline and follow-up, no additional incisional ocular surgery, implant positioned in the supraciliary space, and UBM image passed prospectively defined criteria for image quality by the independent central reader. All outcome measures in the meta-analysis were determined after pooling individual patient data across studies.

As all analyses had exploratory intent, there was no adjustment for multiplicity, neither in terms of multiple endpoints, nor in terms of analyses repeated over time, and there was no adjustment for study heterogeneity. All continuous outcome measures were analyzed using a 2-tailed, paired t-test at a significance level of 5%. The 95% confidence interval and *P*-value were calculated for all postoperative IOP visits, based on patients without missing values. For the main binary outcomes (reduction in IOP $\geq$20%, qualified and complete success), the Wilson's 95% confidence interval was computed.

RESULTS

• **DEMOGRAPHICS AND PATIENT POPULATION:** A total of 82 participants, representing the safety analysis (SAF) population, were enrolled and underwent surgery for MINIject implantation in 3 different clinical trials at 11 sites between June 2017 and June 2019. A flow diagram indicating the flow of patients through the trial can be found in Figure 1. The mean age of the SAF population was 68.6 $\pm$ 9.7 years (36-85 years), with 52.4% being female. In 51.2% of patients, the right eye was the study eye. All patients in the trials had a diagnosis of POAG, with 90.2% of them being classified as mild-to-moderate glaucoma according to their visual field mean deviation ($>$ $-$12 dB). Forty-five percent of patients were pseudophakic. Almost 70% of patients were non-Caucasian, including Hispanic, Black, and Asian patients. There were 79 patients comprising the ITT population at baseline. All performance analyses were conducted on the mITT population at each follow-up timepoint, comprising 73 patients at 6 and 12 months, 69 patients at 18 months, and 66 patients at 24 months. The results of these performance analyses were also confirmed with the PP population, while the safety assessment was conducted on the SAF population. Further demographic details are provided in Table 1.

• **PRIMARY PERFORMANCE OUTCOME:** The mean medicated diurnal IOP at baseline of 23.8 $\pm$ 3.3 mmHg was reduced to 14.4 $\pm$ 4.9 mmHg, 15.6 $\pm$ 4.8 mmHg, 14.6 $\pm$ 4.1 mmHg, and 14.4 $\pm$ 4.5 mmHg at 6, 12, 18, and 24 months, respectively (Figure 2). These results represent an absolute (and relative) reduction of mean diurnal IOP of 9.4 $\pm$ 4.7 mmHg (39.5%), 8.3 $\pm$ 5.2 mmHg (34.4%), 9.17 $\pm$ 4.9 mmHg (37.8%), and 9.6 $\pm$ 5.3 mmHg (39.3%), respectively. All results were statistically significant (*P*-value $<$0.0001 at all timepoints). At 24-month follow-up, the I^2 statistic that reports between study heterogeneity was zero in relation to mean reduction in IOP, providing evidence for a very high level of consistency of outcomes across the 3 MINIject studies in IOP reduction.

• **SECONDARY PERFORMANCE OUTCOME:** The mean number of OHM was reduced from 2.4 $\pm$ 1.1 at baseline to 0.8 $\pm$ 1.2, 1.0 $\pm$ 1.3, 1.3 $\pm$ 1.3, and 1.4 $\pm$ 1.4 at 6, 12, 18, and 24 months, respectively (*P*-value $<$0.0001 at all timepoints) (Figure 2). The proportion of patients free of medication at 6, 12, 18, and 24 months were reported to be 45/73 (61.6%), 38/73 (52.1%), 27/69(39.1%), and 25/66 (37.9%), respectively.

At 24 months in 66 patients, qualified and complete success occurred in 59 (89.4%) and 24 (36.4%) patients, respectively. Kaplan-Meier curves can be found in Figure 3. Mean diurnal IOP was reduced by $\geq$20% in 59 (89.4%) patients with 56 (84.8%) having an IOP $\leq$18 mmHg.

• **SAFETY OUTCOME:** Serious adverse events deemed as related to the MINIject device or the surgical procedure included single reports (1.2% each) of chorioretinal folds, device dislocation, eye pain, lenticular opacities, and papilledema.

Safety events related to the MINIject device/procedure include a reduction in BCVA, defined as a loss of $\geq$3 lines compared to baseline at any time that occurred in 14 patients (17.1%), of which 13 were transient. Of these 13, all cases began in the first postoperative week, 9 resolved in the first month, 3 resolved by month 3, and 1 was due to cataract progression which was addressed with cataract surgery prior to the 18-month visit. Causes of visual acuity loss included hyphema, hemorrhage, anterior segment/chamber inflammation, blurred vision, one case of choroidal detachment, and one case of corneal edema. All visual acuity loss in these 13 patients resolved. In the one additional patient, visual acuity loss from 20/25 to 20/50 began on day 2 and was presumed to be due to postoperative inflammation, anterior chamber cells and corneal edema. The implant dislocated into the anterior chamber on day 2 and was explanted on

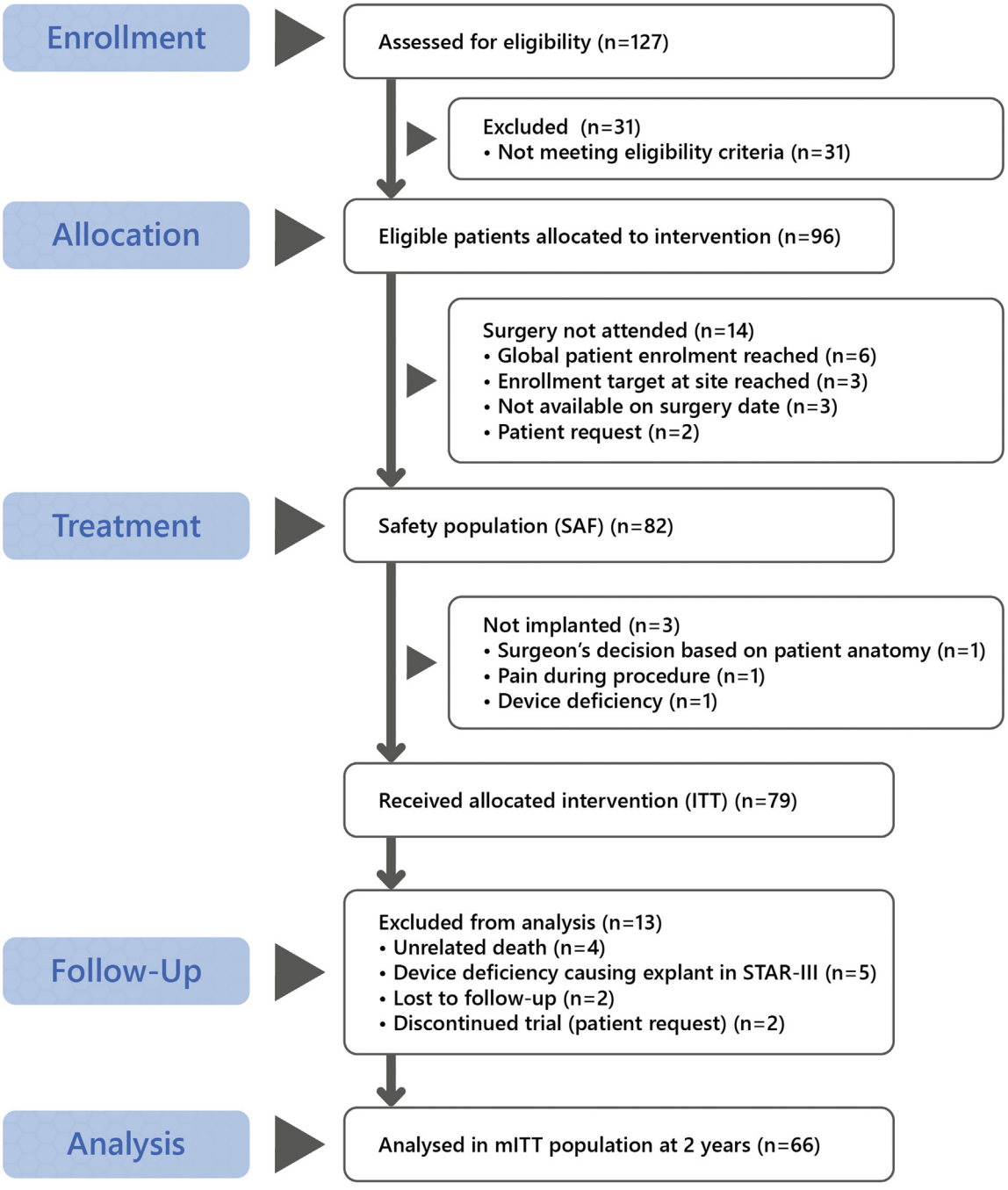

FIGURE 1. Flow diagram indicating the flow of patients through the trial until 2-year follow-up postimplantation. ITT = intention to treat (received implant); mITT = modified ITT (treated with implant and had a measurement of IOP at baseline and follow-up); SAF = safety population (underwent surgery).

day 7. The patient had a mild cataract at baseline which was graded with moderate opacity when the patient discontinued the study on day 70 with visual acuity of 20/40. IOP elevation, defined as an IOP increase ≥10 mmHg at a single visit compared to baseline with an onset after the 1-month visit, occurred in 1 (1.2%) patient. A further 5 events of IOP elevation were reported but were considered not related to the device/procedure. These IOP elevations were resolved with medical treatment in 5 patients; in 1 patient surgical intervention was required with deep sclerectomy followed by 2 laser-assisted goniopunctures, 2 bleb needlings, and cyclophotocoagulation. Two cases (2.4%) of clinical hypotony (IOP < 6 mmHg with clinical signs) were reported and have been previously described.[13,15] The first case was mild transient hypotony which began on day 2 with a duration of 7 days. In the second case, chorioreti-

TABLE 1. Patient Demographics and Clinical Characteristics at Baseline (SAF)

Number of Patients (SAF)		82
Age (mean ± SD)		68.6 ± 9.7 (range, 36-85 years)
Gender	Female	52.4%
	Male	47.6%
Ethnic origin	Caucasian	30.5%
	Hispanic	23.2%
	Black	18.3%
	Asian	17.1%
	Other	11.0%
Pseudophakic		45.1%
Glaucoma type	POAG	100%
Mean central corneal thickness (μ)		529.5 ± 40.0
Mean visual field MD (dB)		-6.0 ± 5.5
Severity of glaucoma	Mild	37.8%
	Moderate	52.4%
	Severe	9.8%
Prior ocular surgery/procedures	Selective laser trabeculoplasty	6.1%
	Vitrectomy	2.4%
Mean IOP ± SD, mmHg[a]		23.8 ± 3.3
Mean number of ocular hypotensive medications ± SD[a]		2.4 ± 1.1

IOP = intraocular pressure; MD = mean deviation; SAF = safety analysis population; SD = standard deviation.
[a]Modified intent-to-treat (mITT) population, n = 79 at baseline.

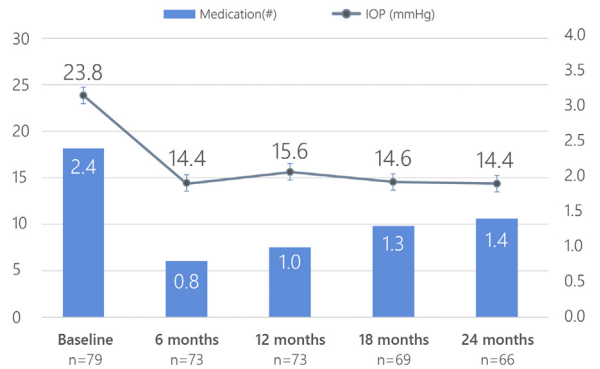

FIGURE 2. IOP and medication reduction between baseline and 24-month follow-up after MINIject implantation. Error bars show 95% confidence intervals. IOP = intraocular pressure; n = number of patients.

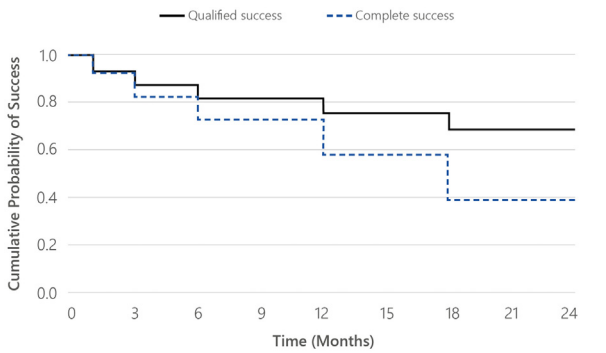

FIGURE 3. Kaplan-Meier curves showing rates of qualified and complete success up to 2 years.

nal folds and an IOP of 5 mmHg were reported on day 32 and were treated on day 88 with a Healon GV injection.

Other frequently reported AEs related to the device/surgery included anterior chamber inflammation (n = 20, 24.4%), hyphema (n = 11, 13.4%) and conjunctival hemorrhage (n = 5, 6.1%). These AEs were mostly transient, and all resolved without sequalae. Of 20 cases of anterior chamber inflammation, 16 were transient and 4 cases persisted beyond the first postoperative month. Of these 4, 1 resolved in the second month, 2 resolved in the third month, and 1 resolved in the fourth month postprocedure. Frequently occurring adverse events (n > 2) in the study eye that were related to the device or procedure are reported in Table 2. There were 5 cases of MINIject explantation reported in a single study (STAR-III), and no explantations reported in the other 2 studies. The explants were associated with the altered (and later abandoned) design of the curvature of the delivery sheath that was used only in this study. Of these, 4 explantations occurred within the first postoperative week, and 1 explantation occurred at 20 days postimplantation. All were related to anterior displacement of the implant into the anterior chamber.

The mean relative reduction in central ECD was 6.2 ± 9.1% at 24 months (n = 41), with no patient showing ≥30% loss in central ECD compared to preoperative measurements.

TABLE 2. Most Frequent (n > 2) Adverse Events in the Study Eye Related to the Device/Procedure in the Safety Analysis Population (n = 82)

Adverse Events Occurring in the Study Eye	Frequency % (n)
Anterior chamber inflammation	24.4% (20)
Reduced visual acuity[a]	17.1% (14)
Hyphema	13.4% (11)
Conjunctival hemorrhage	6.1% (5)
Vision blurred	4.9% (4)
Pupillary deformation	4.9% (4)
Cataract	3.7% (3)

[a]Reduced visual acuity was defined per protocol as loss of ≥3 lines compared to baseline.

DISCUSSION

• **EFFICACY:** This meta-analysis included safety and performance data up to 2-year follow-up for patients implanted with the MINIject glaucoma drainage device into the supraciliary space in a stand-alone procedure from the prospective, multicenter, clinical trials STAR-I, II, and III. The efficacy of MINIject in reducing both IOP and medication-use was meaningful and significant: baseline IOP was reduced from a mean of 23.8 ± 3.3 mmHg on 2.4 ± 1.1 medications to 14.4 ± 4.5 mmHg on 1.4 ± 1.4 medications at 2 years, which represents a mean absolute IOP reduction of 9.6 ± 5.3 mmHg (−39.3%, $P < 0.0001$). There were 89.4% of patients who achieved a ≥20% reduction in IOP compared with baseline, and 37.9% patients were medication-free at 2 years.

MIGS devices provide a safe and effective treatment option when the patient's IOP has not been maintained at target level despite medical management and/or laser trabeculoplasty, or when their glaucoma is nevertheless progressing.[34-36] The introduction of MIGS devices has helped to delay the need for more invasive surgical procedures such as trabeculectomy, which are associated with a higher risk of complications.[37] MIGS devices that deliver an implant have been shown to reduce IOP when implanted stand-alone[12,26,36,38-42] or in conjunction with cataract surgery.[25,43,44] These devices include the iStent (Glaukos Corporation, Laguna Hills, CA, USA) and the Hydrus Microstent (Alcon) that both use the conventional outflow pathway to reduce IOP, and the CyPass Microstent that uses the uveoscleral outflow. Cataract surgery alone is known to reduce IOP by itself,[25,43,44] thus the efficacy of MIGS implants is best assessed in stand-alone settings.

Grisanti et al[26] showed stand-alone efficacy of the suprachoroidal CyPass Microstent in 224 eyes, achieving an IOP reduction from 22.6 ± 6.7 mmHg at baseline on 2.2 ± 1.2 medications to 16.7 ± 3.8 mmHg (−17.7%) on 1.8 ± 1.2 medications at 2 years (n = 120), and to 16.9 ± 4.2 mmHg (−16.9%) on 2.0 ± 1.2 medications at 3 years (n = 112). A ≥20% reduction in IOP compared with baseline was achieved in 56% of pseudophakic eyes and 60% of phakic eyes at 2 years. Better efficacy was demonstrated in the DUETTE trial, where CyPass achieved a reduction of 7.7 mmHg (31.4%) from mean baseline IOP of 24.5 ± 2.8 mmHg on 2.2 ± 1.1 medications to 16.8 ± 3.9 mmHg on 1.5 ± 1.2 medications at 2-year follow-up (n = 37). At 2 years, 56.3% of patients achieved a ≥20% reduction in IOP compared with baseline and 28.6% of patients were medication-free.[12] Results for stand-alone implantation of MINIject compare favorably with that of the CyPass Microstent, which similarly targets the suprachoroidal drainage pathway.

In comparison, glaucoma drainage implants aiming at reestablishing the conventional outflow pathway in a stand-alone procedure have shown mixed efficacy. In the COMPARE trial, 152 eyes were randomized between stand-alone implantation of either 2 first-generation iStents or a Hydrus Microstent, and patients were followed until 12 months.[10] A small IOP reduction in the Hydrus group was significant from baseline to 12 months (19.0 ± 2.5 to 17.3 ± 3.7 mmHg, $P = 0.009$) whilst reduction in the iStent group was not (19.1 ± 3.6 to 18.1 ± 3.7 mmHg, $P = 0.10$). Both treatment arms, however, reduced medication significantly from baseline, with the reduction being significantly greater in the Hydrus group at 12 months (from 2.5 ± 0.7 to 1.0 medications; $P < 0.001$) compared with the iStent group (2.7 ± 0.8 to 1.7 medications; $P < 0.001$), representing a between-group difference of 0.6 medications ($P = 0.004$). At 24 months, 63% of Hydrus patients vs 40% of iStent patients achieved a ≥20% reduction in IOP while on fewer medications, and 38.0% vs 18.7% respectively were medication free.[40]

Better results for the Hydrus Microstent implanted in a stand-alone procedure were seen in a retrospective trial, where Gandolfi et al[38] reported mean baseline IOP of 24 ± 6 mmHg was reduced to 15 ± 3 mmHg on 0.9 ± 0.9 medications 24 months post-intervention (n = 21; $P < 0.001$) with 37% of patients medication free. Similarly, in a prospective stand-alone study of Hydrus, Fea et al[39] reported that mean baseline IOP was reduced from 23.1 ± 5.1 mmHg on 2.3 ±

0.8 medications to 16.5 ± 2.6 mmHg (−6.6 ± 5.6 mmHg; −26%; $P < 0.001$) on 0.9 ± 1.0 medications at the 12-month follow-up (n = 30), with 90% of patients having a ≥20% reduction in IOP from baseline and 47% of patients medication free.

Similar to the COMPARE study, Arnljots et al[41] found a nonsignificant reduction in IOP and no change in medications for the iStent inject implanted in a stand-alone procedure from a baseline of 20.6 ± 5.4 mmHg on 3.0 ± 0.75 medications to 16.0 ± 4.3 mmHg on 3.0 ± 1.1 medications at 2 years ($P = 0.109$ for IOP, $P = 0.451$ for medication). In a retrospective study, Pahlitzsch et al[36] showed that iStent inject implanted in 66 eyes reduced IOP from 19.5 ± 2.0 mmHg at baseline to 15.5 ± 2.3 mmHg at 2 years and 13.8 ± 2.7 mmHg (−29.9%; $P < 0.001$) at 3 years, with no significant reduction in medications at 3 years (2.2 ± 1.2 to 1.7 ± 1.5; $P = 0.612$). In contrast, Hengerer et al[42] reported better results for iStent inject implanted in a stand-alone procedure with baseline IOP of 25.3 ± 6.0 mmHg on 3.0 ± 0.9 medications. IOP was reduced to 15.0 ± 2.7 mmHg ($P < 0.0001$) at 2 years (n = 36) and to 14.6 ± 2.0 mmHg (−42%; $P < 0.0001$) on 0.6 ± 0.8 medications at 3 years (n = 33), with 87.9% of eyes achieving an IOP reduction of ≥20% at 3 years, and with 53% and 61% of patients medication free at 2 and 3 years, respectively. Possible explanations for these mixed efficacy results in the conventional outflow pathway have been given above.[15,19-24] The present results suggest that the MINIject supraciliary device may be more effective at 2-year follow-up than MIGS which target the conventional outflow to lower IOP.

• **SAFETY:** There were no unanticipated adverse events related to the MINIject device or surgical procedure. The most frequently reported adverse events were anterior chamber inflammation (24.4%), reduced visual acuity (17.1%), hyphema (13.4%), and conjunctival hemorrhage (6.1%). The nature and frequency of these AEs is similar to those reported after implantation of other MIGS devices and in glaucoma surgery in general. These AEs were mostly transient (<30 days) and all resolved without sequalae, except one case of visual acuity loss where the patient exited the study at day 70. The rates of clinical hypotony and IOP elevation after MINIject implantation were low (2.4% and 1.2% respectively). When comparing with other MIGS implants, anterior chamber inflammation was reported in the range of 0.9% to 7.3%[10,26,27] and reduced visual acuity ranged from 2.7% to 9.7%.[10,12,26,27,39] Hyphema was reported with rates of 1.3% to 19.0%.[26,27,38] Rates of IOP increase ranged from 4.1% to 18.2%.[10,12,26,27,39]

In 2018, the CyPass Microstent was withdrawn from the market due to safety concerns regarding ECD loss 5 years after implantation.[29] Further analysis determined that the cause was most likely improper anterior positioning of the CyPass implant in the anterior chamber.[28] In all 3 trials of MINIject included in this meta-analysis, ECD was prospectively collected up until 2 years.[13-15] In addition, the MINIject implant is soft and flexible, and has a green marker to guide correct positioning. In this meta-analysis, mean central ECD loss was found to be 6.2% 2 years postimplantation of MINIject, which is less than the rate of 10.0% to 12.3% 2 years after cataract surgery alone, as reported to the FDA from pivotal trials.[45-47] In addition, no single patient treated with MINIject in this meta-analysis had an ECD loss >30% at 2 years, while rates of 7.2% to 9.5% have been seen after cataract surgery alone.[45-47] ECD loss is rarely reported in stand-alone trials of other MIGS devices which makes comparison with other MIGS implants difficult,[12,26,36,38-42] however the mean ECD loss of MINIject is favorable compared to a loss of 13% to 14% reported after phaco-MIGS procedures at 2 years.[45-47]

• **LIMITATIONS:** One advantage of pooling these 3 trials into a meta-analysis is that treatment with MINIject was performed over a wide geographical area in patients of different ethnicities and with a larger number of sites, surgeons and patients than is reported for each of the single trials. However, despite the underlying MINIject trials having very similar trial designs to each other, the design of a meta-analysis has limitations compared with a randomized trial, thus not allowing for comparative conclusions on safety and performance with other MIGS implants. In addition, comparison between MIGS trials is challenging due to diverse population demographics between the studies, differing baseline IOPs, and the divergent ways that outcomes are reported and at various time periods.

Although the implant was identical in all 3 MINIject trials, a different delivery system was used between trials, and thus safety events associated with the different delivery systems could not be distinguished in this meta-analysis. Also related to the surgical procedure, the MINIject trials were all pre-market studies carried out prior to commercial approval, resulting in a learning curve for surgeons as they used MINIject for the first time. In contrast, the MIGS stand-alone comparative studies were all carried out post-commercialization, and thus surgeons were likely already experienced with the devices and may not have experienced a learning curve in the results reported.

Finally, larger trials with longer durations, preferably randomized to alternative MIGS implants, are necessary to fully evaluate the safety and efficacy of the MINIject supraciliary glaucoma implant in comparison with other MIGS devices.

CONCLUSION

In conclusion, the outcomes of this meta-analysis, which assessed the MINIject supraciliary glaucoma drainage implant up to 2 years after implantation in a stand-alone procedure, confirm the favorable performance and safety profile of MINIject. MINIject can be considered a valuable surgical

treatment option for mild to moderate glaucoma patients, and an effective alternative to other MIGS up to 2 years after implantation.

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Funding/Support: iSTAR Medical (Wavre, Belgium) participated in and provided funding for the design and conduct of the STAR-I, II, III trials; the collection, management, and analysis of data; and the preparation of the manuscript.

Financial Disclosures: **Iqbal Ike K. Ahmed:** Aequus (C), Ace Vision (C), Aerie Pharmaceuticals (C, R), Akorn (C), Alcon (C, L, R), Allergan (C, L, R), American Academy of Ophthalmology Board (M), Aquea Health, Inc (C), ArcScan (C), Avellino Lab USA, Inc (C), Avisi (C), Bausch Health (C), Beaver Visitec (C), Belkin Vision (C), Beyeonics (C), Bionode (C, R), Carl Zeiss Meditec (C, L), Centricity Vision, Inc (C), CorNeat Vision (C), Custom Surgical (C), Elios Vision (C), ElutiMed (C), Equinox (C), eyeFlow, Inc (C), EyedMed (C), EyeQ Technologies (C), Exhaura Limited (C), Genentech (C), Glaukos (C, R), Gore (C), Heine (C, L), Heru (C), Hexiris Pharma (C), Iantrek (C), InjectSense (C), Iridex (C), iCare (R), iSTAR Medical (C), Ivantis (C, R), Johnson & Johnson Vision (C, L, R), Labtician Thea (C), LayerBio (C), Leica Microsystems (C), Life Long Vision (C), Long Bridge Medical, Inc (C), MicroOptx (C), MST Surgical (C, L), Myra Vision/Shifamed LLC (C), New World Medical (C, R), NovaEye (C), Ocular Instruments (C), Ocular Therapeutix (C), Oculo (C), Oculus Surgical (C), Omega Ophthalmics (C), PolyActiva (C), PulseMedica (C), Radiance Therapeutics, Inc (C), Radius XR (C), Rheon Medical SA (C), Ripple Therapeutics (C), Samsara Vision (C), Sanoculis (C), Santen (C, R), Singapore Biodesign Programme Office (C), Sight Sciences (C), Smartlens, Inc (C), Stroma (C), Thea Pharma (C), TFS Health Science (C), ViaLase (C), Visus Therapeutics (C), Vizzario (C), VSY Biotechnology (C), Zilia, Inc (C); **Philippe Denis:** Alcon (C, L), Glaukos (C, L), Santen (C); **H. Burkhard Dick:** AcuFocus Inc. (C, S), Atia Medical Inc. (M, C), Avellino Lab. Inc. (M, C), Bausch + Lomb Inc. (L), Bayer Vital GmbH (R), ESCRS secretary (M), EuroEyes (C), EXCEL-LENS Inc. (C, S), Eyesafe (M), Eyra Inc. (M), Healthe LLC (M, S), Hoya GmbH (R), Infinite Vision Optics SAS (M), IOP Implandata GmbH (R, S), iSTAR Medical SA (C, R), Johnson & Johnson Vision (C, R, L, P), MicroOptx (C, R), Morcher GmbH (R, P), Novartis Pharma GmbH (R), Oculus Inc. (C, Y), Orasis Pharmaceuticals Ltd (S), Percept Corporation (M), Rowiak GmbH (R), RxSIGHT Inc. (C, R, S), Stroma Medical Corp. (S), Treasurer of the GSCRS (DGII) (M), Vivior AG (M, S), WebMD LLC (M), Zebra Biologics Inc. (R); **Antonio M. Fea:** AbbVie (C, R, L), EyeD pharma (C, M), Glaukos (M), Santen (C); **Brian E. Flowers:** Alcon (C), Glaukos (C), iSTAR Medical (C), New World Medical (C), NiCox (C), Sanoculis (C), Sight Sciences (C); **Christoph Hirneiss:** AbbVie (S), Glaukos (L), iSTAR Medical, Novartis (S), Santen (C); **Kaweh Mansouri:** AbbVie (C), Alcon (S), Fabrinal (C), ImplanData (C), iSTAR Medical (C), New World Medical (C), Oertli (C), Santen (C), Théa Pharma (C); **Marc J. Mackert:** AbbVie (C, L, M, T), Allergan (L), Implandata Ophthalmic Products GmbH (R), Iridex (D), iSTAR Medical (C), Santen (C, E), Sight Sciences (E, L), Thea (L); **I. Paul Singh:** iSTAR Medical (C,L), Alcon (C,L), Allergan (C,L), B+L (C,L), Glaukos (C,L), New World Medical (C,L), Nova Eye (C,L), Sight Sciences (C,L), Thea (L), Viatris (L).

C: Consulting fees, D: Device provision, E: Expert testimony, L: Lectures, M: Data safety monitoring or advisory board, P: Patent, R: Grant, S: Stock or options, T: Travel, Y: Royalties.

All authors attest that they meet the current ICMJE criteria for authorship.

Meeting Presentation: the data in this manuscript were presented in part at the European Glaucoma Society (EGS) congress 2022 in Athens, Greece, and at the American Glaucoma Society (AGS) meeting 2023 in Austin, Texas.

Acknowledgments: The authors acknowledge the independent members of the Safety Monitoring Committee A.G. Jünemann MD (Augenzentrum Erlangen, Erlangen, Germany), R.D. Fechtner MD (SUNY Upstate Medical University, NY, USA), R.A. Eiferman MD (University of Louisville, Louisville, USA), L.H. Silver PhD (Silver Pharma Consulting Inc., El Paso, Texas, USA). The authors thank A. Kroker PhD (Optana, Großostheim, Germany) for clinical trial and data management, and manuscript writing; D.K.I Seh (IDDI, Louvain-la-Neuve, Belgium) for statistical services; and K. Awad BSc. MBA (Gold Coast, Australia) for manuscript writing and editing.

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